

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

0 178 139
A3

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 85307152.0

(22) Date of filing: 07.10.85

(51) Int. Cl.⁴: **C 07 C 177/00, C 07 F 7/18,**
C 07 C 49/753, C 07 C 49/517

(30) Priority: 08.10.84 JP 209629/84
09.11.84 JP 235307/84
18.02.85 JP 28430/85

(43) Date of publication of application: 16.04.86
Bulletin 86/16

(84) Designated Contracting States: CH DE FR GB IT LI SE

(88) Date of deferred publication of search
report: 27.05.87 Bulletin 87/22

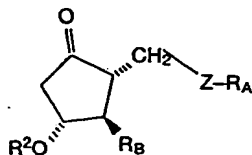
(71) Applicant: **TEIJIN LIMITED, 11 Minamihonmachi 1-chome**
Higashi-ku, Osaka-shi Osaka 541 (JP)

(72) Inventor: **Noyori, Ryoji, 135-417, Umemori Shinden**
Nisshin-cho, Aichi-gun Aichi-ken (JP)
Inventor: **Suzuki, Masaaki, 2-66, Yata-machi Higashi-ku,**
Nagoya-shi Aichi-ken (JP)
Inventor: **Tanaka, Toshio, 6-17-20, Tamadaira, Hino-shi**
Tokyo (JP)
Inventor: **Kurozumi, Seizi, 1-2-28 Higashitokura,**
Kokubunji-shi Tokyo (JP)

(74) Representative: **Myerscough, Philip Boyd et al,**
J.A.Kemp & Co. 14, South Square Gray's Inn, London,
WC1R 5EU (GB)

(54) **Process for producing 2,3-disubstituted -4-substituted cyclopentanones, enantiomorphs, or mixtures thereof.**

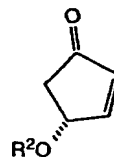
(57) Process for producing a 2,3-disubstituted-4-substituted cyclopentanone, an enantiomorph thereof, or a mixture of these in an arbitrary ratio, which process comprises producing a 2,3-disubstituted-4-substituted cyclopentanone represented by the formula



(6)

R² represents a tri(C₁-C₇)hydrocarbon silyl group or R²O represents an acetal linkage, R₈ represents a substituted or unsubstituted C₂-C₁₀ alkyl or alkenyl group, Z represents an ethylene, ethynylene, trans-vinylene, cis-vinylene, phenylene or phenyleneoxa group, and R_A represents a hydrogen atom or a substituted or unsubstituted C₁-C₇ alkyl or alkenyl group, an enantiomorph thereof, or a mixture of these in an arbitrary ratio, which comprises

(A) subjecting a 4-substituted-2-cyclopentenone represented by the following formula



(1)

wherein R² is as defined above, an enantiomorph thereof, or a mixture of these in an arbitrary ratio, and an organocopper compound formed from an organolithium compound represented by the following formula



wherein R_B is as defined above, and a copper compound represented by the following formula



wherein Q represents a halogen atom, a cyano group, a phenylthio group or a 1-pentynyl group, to conjugate addition-reaction, and thereafter,

(B) reacting the resulting enolate intermediate with a halide represented by the following formula

(Continuation next page)



wherein Z and R_A are as defined above, and X represents a halogen atom or a tosyl group, in the presence of an organotin compound represented by the following formula



wherein R's are identical or different and each represents a C₁-C₄ alkyl group, a C₃-C₇ cycloalkyl group, a phenyl group or a halogen atom provided that two or three R's cannot be halogen atoms at the same time, and Y represents a halogen atom or a triflate group.



European Patent
Office

EUROPEAN SEARCH REPORT

0178139

Application number

EP 85 30 7152

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
Y,D	TETRAHEDRON LETTERS, vol. 25, no. 23, 1984, pages 2487,2488, Pergamon Press LTD, Oxford, GB; H. NISHIYAMA et al.: "Conjugate addition of lithiotrimethylsilylacetate. A simple synthesis of methyl jasmonate via vicinal double alkylation" * Whole article *	1-3,5 7,9,10	C 07 C 177/00 C 07 F 7/18 C 07 C 49/753 C 07 C 49/517
Y,D	--- TETRAHEDRON LETTERS, vol. 25, no. 2, 1984, pages 223-226, Pergamon Press Ltd, Oxford, GB; H. NISHIYAMA et al.: "New stereocontrolled aproach to some insect pheromones via silicon-directed Beckmann fragmentation" * Page 224 *	1-3,5 7,9,10	
P,Y	--- EP-A-O 133 450 (MILES LABORATORIES) * Pages 13-15; page 28, point IX; claims * -----	1-10	C 07 C
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 29-01-1987	Examiner BERTE M.J.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	



Europäisches Patentamt
European Patent Office
Office européen des brevets

Publication number:

**0 178 139
A2**

12

EUROPEAN PATENT APPLICATION

21 Application number: 85307152.0

22 Date of filing: 07.10.85

51 Int. Cl.: **C 07 C 177/00, C 07 F 7/18,
C 07 C 49/753, C 07 C 49/517**

30 Priority: 08.10.84 JP 209629/84
09.11.84 JP 235307/84
18.02.85 JP 28430/85

43 Date of publication of application: 16.04.86
Bulletin 86/16

84 Designated Contracting States: CH DE FR GB IT LI SE

71 Applicant: **TEIJIN LIMITED,**
11 Minamihonmachi 1-chome Higashi-ku, Osaka-shi
Osaka 541 (JP)

72 Inventor: **Noyori, Ryoji, 135-417, Umemori Shinden
Nisshin-cho, Aichi-gun Aichi-ken (JP)**
Inventor: **Suzuki, Masaaki, 2-66, Yata-machi Higashi-ku,
Nagoya-shi Aichi-ken (JP)**
Inventor: **Tanaka, Toshio, 6-17-20, Tamadaira, Hino-shi
Tokyo (JP)**
Inventor: **Kurozumi, Seizi, 1-2-28 Higashitokura,
Kokubunji-shi Tokyo (JP)**

74 Representative: **Myerscough, Philip Boyd et al, J.A.Kemp
& Co. 14, South Square Gray's Inn, London, WC1R 5EU
(GB)**

54 Process for producing 2,3-disubstituted -4-substituted cyclopentanones, enantiomorphs, or mixtures thereof.

57 A process for producing a 2,3-disubstituted-4-substituted cyclopentanone, an enantiomorph thereof, or a mixture of these in an arbitrary ratio, which process comprises (A) subjecting a 4-substituted-2-cyclopentenone, an enantiomorph thereof, or a mixture of these in an arbitrary ratio, and an organocopper compound to conjugate addition-reaction, and thereafter (B) reacting the resulting enolate intermediate with a halide in the presence of an organotin compound.

EP 0 178 139 A2

- 1 -

PROCESS FOR PRODUCING 2,3-DISUBSTITUTED-4-SUBSTITUTED
CYCLOPENTANONES, ENANTIOMORPHS, OR MIXTURES THEREOF

This invention relates to a process for producing 2,3-disubstituted-4-substituted cyclopentanones, enantiomorphs, or mixtures thereof.

Natural prostaglandins (prostaglandin will be abbreviated hereinafter as PG) are known as local hormones (autacoid) having high biological and pharmacological activities. In an attempt to develop new medicines by skillfully utilizing these physiological characteristics of PGs, not only natural PGs but various derivatives thereof have been studied.

Natural PGE_2 and PGF_2 as typical compounds of PGE and PGFs have the activity of contracting the smooth muscles of the uterus, and are used as most useful labor inducing agents. Natural PGE_1 , on the other hand, is a type-L prostaglandin and has unique biological activities such as platelet aggregation inhibiting activity and blood pressure lowering activity. In recent years, natural PGE_1 has been used as an agent for treating peripheral vascular diseases in the cardiovascular therapeutic field.

A number of methods have heretofore been known for obtaining these PGEs and PGFs [see J. B. Bindra et al.; Prostaglandin Synthesis, Academic Press (1977)]. Typical examples of such methods are listed below.

(i) Biosynthesis from arachidonic acid or di-homo-gamma-linolenic acid [see B. Samuelson et al. Angev. Chem. Int. Ed. Engl. 4, 410 (1965)].

(ii) Synthesis via the Corey lactone which is an important key-intermediate [see E. J. Corey et al., J. Amer. Chem. Soc., 92, 397 (1970)].

(iii) Synthesis through a 2-substituted-2-cyclopentenone which is also an important intermediate [see C. J. Sih et al., J. Amer. Chem. Soc., 97, 865 (1975)].

(iv) Selective reduction of 5,6-dehydro- PGE_2 or

PGF_{2α} [see E. S. Ferdinandi et al., Can. J. Chem., 49, 1070 (1971); and C. H. Lin et al., Prostaglandin, 11, 377 (1976)].

According to the biosynthetic method (i), the starting poly-unsaturated fatty acid is difficult to procure. Moreover, the yield of the desired product from this starting material is very low, and it is difficult to isolate it in pure form from the by-products. In the chemical synthetic methods (ii) to (iv), many steps are required for obtaining the starting materials. Even when the starting materials are easily available, the production of prostaglandins from them requires many steps, and the total yields of the prostaglandins are still very low. Hence, these methods are still desired to be improved.

In an attempt to overcome the various difficulties of these methods, a three-component coupling process for the synthesis of a PG skeleton was proposed which involves conjugate addition to a 2-cyclopentenone compound followed by a step of trapping the enolate [see G. Stock et al., J. Amer. Chem. Soc., 97, 6260 (1975), and K. G. Untch et al., J. Org. Chem. 44, 3755). This process, however, has the difficulty that it has to go through many steps in which formaldehyde, a low molecular compound, is used to trap the enolate and the PG skeleton is synthesized chemically through the resulting important intermediate, and that the total yield of the desired product is low.

On the other hand, the following methods have been proposed for more efficient production of the PG skeleton by the three-component coupling process.

(1) Japanese Laid-Open Patent Publications Nos. 96542/1975 and 101337/1975, G. H. Posner et al., Tetrahedron Letters, 2591 (1974), and G. H. Posner et al., J. Amer. Chem. Soc., 97, 107 (1974).

These documents disclose a method for producing 2,3-disubstituted cyclopentanones by conjugate addition of

- 3 -

an organocopper compound to 2-cyclopentenone and subsequent alkylation of the reaction product with halides. These document, however, fail to give a working example covering the production of prostaglandins and only describe a working example carried out in a model system. None of them disclose an example of producing 2,3-disubstituted-4-substituted cyclopentanones from 4-substituted-2-cyclopentenones.

(2) J. W. Patterson, Jr. and J. H. Fried., J. Org. Chem., 39, 2506 (1974).

The authors successfully synthesized 11-deoxy-prostaglandin E₁ by applying the method (1) to 2-cyclopentenones. However, they do not disclose even the possibility of producing 2,3-disubstituted-4-substituted-cyclopentanones from 4-substituted-2-cyclopentenones.

(3) G. Stork and M. Isobe, J. Am. Chem. Soc., 97, 6260 (1975).

The authors succeeded in conjugate addition of an organocopper compound to a 4-substituted-2-cyclopentenone and trapping the resulting enolate by monomeric formaldehyde. But they gave a negative conclusion about the alkylation reaction of trapping the enolate with an alkylating agent.

(4) J. A. Noguez and L. A. Maldonado, Synthetic Communications, 6, 39 (1976).

According to the method disclosed in this document, a lithium salt of cyanohydrin whose part corresponding to the omega-chain of prostaglandin is protected is introduced into 2-cyclopentenone by conjugate addition, and the resulting enolate is captured by a propargyl halide to obtain a 11-deoxyprostaglandin derivative. However, it does not even disclose the possibility of producing 2,3-disubstituted-4-substituted-cyclopentanones from 4-substituted-2-cyclopentenones.

(5) R. Davis and K. G. Untch, J. Org. Chem., 44, 3755 (1979).

- 4 -

The authors stated that various investigations were made in an attempt to add an organocopper compound having an organic group corresponding to the omega-chain of prostaglandin to a 4-substituted-2-cyclopentenone by conjugate addition, and to alkylate the resulting enolate directly with an allyl halide, but all of the attempts were unsuccessful.

(6) A. J. Dixon and R. J. K. Taylor, J. Chem. Soc., Parkin I, 1407 (1981).

10 The authors challenged the allylation of an enolate formed from 2-cyclopentenone and an organocopper compound which had been considered to be difficult of proceeding, and succeeded in obtaining an intermediate for the synthesis of 11-deoxyprostaglandin. They, however, 15 failed to disclose anything about a specific example, or even the possibility, of a process for producing 2,3-disubstituted-4-substituted cyclopentanones from 4-substituted-2-cyclopentenones.

(7) Nishiyama et al., Tetrahedron Letters, 25, 20 223 (1984) and 25, 2487 (1984).

The authors succeeded in introducing trimethylsilyllithium or methyllithiotrimethylsilyl acetate into 2-cyclopentenone by conjugate addition, adding tributyltin chloride, and thereafter alkylating the enolate with a 25 propargyl bromide derivative. But they failed to disclose a specific example, or even the possibility, of a process for producing 2,3-disubstituted-4-substituted cyclopentanones from 4-substituted-2-cyclopentenones.

For the prior art techniques (1) to (7) and the 30 other prior techniques, reference may be made to a general synthesis entitled (Prostaglandin Syntheses by Three-Component Coupling" by Ryoji Noyori et al. in Angewandte Chemie, International Edition in English, 23, No. 11, November 1984, pages 847-876.

35 It is an object of this invention to provide a novel process for producing 2,3-disubstituted-4-substituted

- 5 -

cyclopentanones, enantiomorphs thereof, or mixtures thereof.

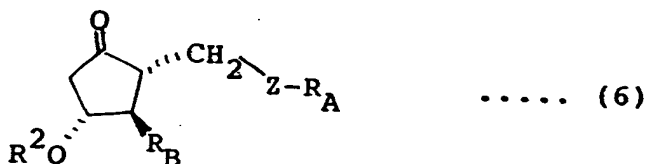
Another object of this invention is to provide a process for efficiently producing 2,3-disubstituted-4-substituted cyclopentanones such as PGEs, enantiomorphs thereof, or mixtures thereof.

Still another object of this invention is to provide a process for producing a 2,3-disubstituted-4-substituted cyclopentanone easily in high yields in one step or a single pot on the basis of the present inventors' discovery that the 2,3-disubstituted-4-substituted cyclopentanone, which cannot be produced via a lithium enolate or copper enolate in the prior art, can now be produced via a tin enolate.

A further object of this invention is to provide a novel process for producing 2,3-disubstituted-4-substituted cyclopentanones in one step or a single pot on the basis of the present inventors' discovery that when the 4-substituted-2-cyclopentenone and an organocopper compound are subjected to conjugate addition reaction and the resulting copper enolate is converted to a tin enolate in situ, the tin enolate can be directly reacted with an alkyl halide or an alkenyl halide.

Other objects and advantages of this invention will become apparent from the following description.

According to this invention, the above objects and advantages of this invention are achieved by a process for producing a 2,3-disubstituted-4-substituted cyclopentanone represented by the following formula

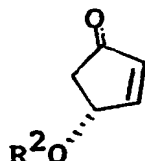


R^2 represents a tri(C_1 - C_7)hydrocarbon silyl group or R^2O represents an acetal linkage, R_B

- 6 -

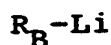
represents a substituted or unsubstituted C_2-C_{10} alkyl or alkenyl group, Z represents an ethylene, ethynylene, trans-vinylene, cis-vinylene, phenylene or phenyleneoxa group, and R_A represents a hydrogen atom or a substituted or unsubstituted C_1-C_7 alkyl or alkenyl group, an enantiomorph thereof, or a mixture of these in an arbitrary ratio, which comprises

(A) subjecting a 4-substituted-2-cyclopentenone represented by the following formula



..... (1)

wherein R^2 is as defined above, an enantiomorph thereof, or a mixture of these in an arbitrary ratio, and an organocopper compound formed from an organolithium compound represented by the following formula



..... (2)

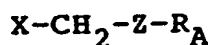
wherein R_B is as defined above, and a copper compound represented by the following formula



..... (3)

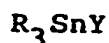
wherein Q represents a halogen atom, a cyano group, a phenylthio group or a 1-pentynyl group, to conjugate addition-reaction, and thereafter,

(B) reacting the resulting enolate intermediate with a halide represented by the following formula



..... (5)

wherein Z and R_A are as defined above, and X represents a halogen atom or a tosyl group, in the presence of an organotin compound represented by the following formula



..... (4)

wherein R's are identical or different and each represents a C₁-C₄ alkyl group, a C₃-C₇ cycloalkyl group, a phenyl group or a halogen atom provided that two or three R's cannot be halogen atoms at the same time, and Y represents a halogen atom or a triflate group.

The process of this invention comprises a conjugate addition-reaction step (A) of reacting the 4-substituted-2-cyclopentenone (1), or an enantiomorph thereof, or a mixture of these, with the organocopper compound formed from the organolithium compound (2) and the copper compound (3), and the step (B) of reacting the enolate intermediate formed in step (A) with the halide (5) in the presence of the organotin compound (4).

The 4-substituted-2-cyclopentenone used as a starting material in this invention is represented by formula (1). R² in formula (1) represents a tri(C₁-C₇)-hydrocarbon silyl group or a group forming an acetal linkage (OR²) together with the oxygen atom of the hydroxyl group.

Examples of the tri(C₁-C₇)hydrocarbon silyl group include tri(C₁-C₄)alkylsilyl groups such as trimethylsilyl, triethylsilyl, triisopropylsilyl and t-butyldimethylsilyl groups, and diphenyl(C₁-C₄)alkylsilyl groups such as diphenylmethylsilyl and t-butyldiphenylsilyl groups, and phenyl di(C₁-C₄)alkylsilyl groups such as phenyldimethylsilyl group and tribenzylsilyl group. Among these, the t-butyldimethylsilyl group is especially preferred.

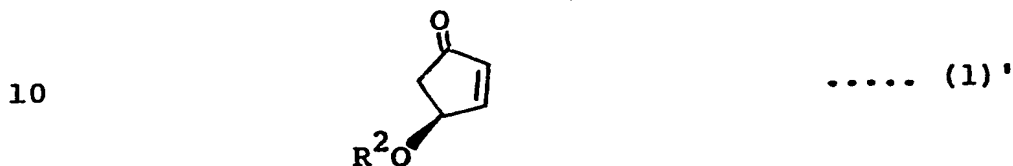
Examples of the group which forms an acetal linkage together with the oxygen atom of the hydroxyl group include methoxymethyl, 1-ethoxyethyl, 2-methoxy-2-propyl, 2-ethoxy-2-propyl, (2-methoxyethoxy)methyl, benzyloxymethyl, 2-tetrahydropyranyl, 2-tetrahydrofuranyl, and 6,6-dimethyl-3-oxa-2-oxobicyclo[3.1.0]hex-4-yl groups. Of these, the

- 8 -

2-tetrahydropyranyl, 2-tetrahydrofuranyl, 1-ethoxyethyl, 2-methoxy-2-propyl, (2-methoxyethoxy)methyl and 6,6-dimethyl-3-oxa-2-oxobicyclo[3.1.0]hex-4-yl groups are preferred.

5 Specific examples of the compound of formula (1) will be apparent from the definition of R^2 and its specific examples given above.

 The enantiomorph of the compound of formula (1) is represented by the following formula (1)'



wherein R^2 is as defined above.

 The 4-substituted-cyclopentenone used as the starting material in step (A) is a compound of formula (1) or (1)', or a mixture of the compounds (1) and (1)' in
15 arbitrary ratios. An equimolar mixture of the compounds of formula (1) and (1)' is a racemic mixture, and a mixture of these in different proportions shows varying degrees of specific rotation according to their mixing ratios.

R_B in formula (2) representing the organolithium
20 compound represents a substituted or unsubstituted C_2-C_{10} alkyl or alkenyl group.

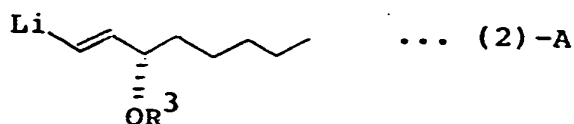
 The unsubstituted C_2-C_{10} alkyl group may be linear or branched, and includes, for example, ethyl, propyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, hexyl,
25 heptyl, octyl, nonyl and decyl groups.

 The unsubstituted C_2-C_{10} alkenyl group may be linear or branched, and includes, for example, vinyl, 1-propenyl, 1-butenyl, 1-pentenyl, 1-hexenyl, 1-heptenyl, 1-octenyl, 1-nonyl and 1-decyl group. They may be isomers
30 of either E or Z type.

 Examples of the substituent on the substituted C_2-C_{10} alkyl group for R_B are C_3-C_7 cycloalkyl groups,

Examples of the substituent on the substituted C_2-C_{10} alkenyl group for R_B include C_1-C_4 alkyl groups, C_3-C_7 cycloalkyl groups, C_2-C_4 alkynyl groups, a phenyl group and a phenoxy groups (the phenyl and phenoxy groups may further be substituted by fluoro, methyl, trifluoromethyl or trifluoromethoxy), C_1-C_4 alkoxy groups and groups of the formula OR^2 where R^2 is as defined above.

Specific examples of the organolithium compound (2) having such a substituted or unsubstituted alkyl or alkenyl group having 2 to 10 carbon atoms will be apparent from the specific examples of R_B given above. Compounds represented by the following formula



wherein R^3 represents a tri(C_1 - C_7)hydrocarbon

- 10 -

silyl group or OR^3 represents an acetal linkage,
are especially preferred.

The sole reason for the preference of the organolithium compounds of formula (2)-A is that they partly
5 agree with the skeleton of natural prostaglandin.

Q in formula (3) representing the copper compound represents a halogen atom such as chlorine, bromine or iodine atom, a cyano group, a phenylthio group or a 1-pentenyl group.

10 Examples of the copper compound will be apparent from the definitions of Q above.

In the conjugate addition reaction step (A) of the present invention, the organocopper compound formed from the organolithium compound (2) and the copper compound
15 (3) is used.

The organocopper compound from the organolithium compound (2) and the copper compound (3) can be obtained by the methods described, for example, in G. H. Posner, Organic Reaction, vol. 19, 1 (1972); and Noyori et al.,
20 Tetrahedron Letters, 21, 1247 (1980), 23, 4057 (1982), 23, 5563 (1982), 24, 1187 (1983), 24, 4103 (1983), 25, 1383 (1984), and Isr. J. Chem., 24, 118 (1984). The descriptions of these literature references may be cited as part of the disclosure of the present specification.

25 For example, the organocopper compound may be prepared by reacting the organolithium compound and a copper salt in an inert solvent, for example a hydrocarbon such as benzene, hexane or heptane or an ether such as diethyl ether or dimethoxyethane at room temperature to
30 $-78^{\circ}C$ for not more than several hours, for example for 0.5 hour at $-78^{\circ}C$.

Preferably, the conjugate addition reaction in step (A) is caused to proceed smoothly by using a trivalent organophosphorus compound, for example a trialkylphosphine
35 (such as triethylphosphine or tributylphosphine), a trialkyl phosphite (such as trimethyl phosphite, triethyl

- 11 -

phosphite, triisopropyl phosphite or tri-n-butyl phosphite), hexamethylphosphoric triamide or triphenyl phosphine. Tributylphosphine, and hexamethylphosphoric triamide can be preferably used.

5 The step (A) of the process of this invention is carried out advantageously by reacting the 4-substituted-2-cyclopentenone represented by formula (1) with the organocopper compound in the presence of the trivalent organophosphorus compound and an aprotic inert organic
10 medium.

 The 4-substituted-2-cyclopentenone and the organocopper compound stoichiometrically react in equimolar proportions. Usually, 0.5 to 2.0 moles, preferably 0.8 to 1.5 moles, especially preferably 1.0 to 1.3 moles, of the
15 organocopper compound is used per mole of the 4-substituted-2-cyclopentenone.

 The reaction in step (A) is carried out at a temperature of, for example, -100 to 20°C , preferably -78°C to 0°C . The reaction time varies depending upon the re-
20 action temperature. Usually, the reaction proceeds sufficiently if it is carried out at -78 to -20°C for about 1 hour.

 Advantageously, the reaction is carried out in the presence of an organic medium. Suitable organic media
25 are inert and aprotic and do not react with the reagents.

 Examples of the aprotic inert organic media include saturated hydrocarbons such as pentane, hexane, heptane and cyclohexane; aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as diethyl ether,
30 tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether, and aprotic polar solvents such as hexamethylphosphoric triamide (HMP), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAC), dimethyl sulfoxide, sulfolane and N-methylpyrrolidone. These media may be used
35 as a mixture of two or more. The inert medium used to produce the organocopper compound may be directly used as

- 12 -

the aprotic inert organic medium. In this case, the 4-substituted-2-cyclopentenone is added to the reaction

system in which the organocopper compound has been produced, and then the reaction is carried out. The amount of
5 the organic medium may be that which is sufficient to allow the reaction to proceed smoothly. Usually, it is 1 to 100 times, preferably 2 to 20 times, the weight of the 4-substituted-2-cyclopentenone.

The trivalent organic phosphorus compound may be
10 caused to be present during the preparation of the organocopper compound, and the 4-substituted-2-cyclopentenone may be added to this reaction system and then reacted.

Consequently, in step (A) of the process of this invention, a "conjugate added enolate" in which the organic
15 group moiety R_B adds to the 3-position of the 4-substituted-2-cyclopentenone is formed.

In step (B) of the process of this invention, the resulting enolate is reacted with the halide of formula (5) in the presence of the organotin compound of formula (4).

20 In formula (4) representing the organotin compound, the three R's are identical or different and each represents an alkyl group having 1 to 4 carbon atoms, a cycloalkyl group having 3 to 7 carbon atoms, a phenyl group, or a halogen atom. The two or three R's are not
25 simultaneously halogen atoms.

According to the definition of R, examples of the organotin compound include $\text{tri}(\text{C}_1\text{-C}_4)\text{alkyltin}$ chlorides such as trimethyltin chloride, trimethyltin bromide, triethyltin bromide, tripropyltin chloride, tributyltin
30 chloride and tributyltin bromide; $\text{tri}(\text{C}_1\text{-C}_4)\text{alkyltin}$ bromides; dialkyltin dihalides such as dimethyltin dichloride, diethyltin dichloride and dibutyltin dichloride; tributyltin triflate; $\text{tri}(\text{C}_3\text{-C}_7)\text{cycloalkyltin}$ halides such as tricyclohexyltin chloride, tricyclohexyltin bromide,
35 tricyclopentyltin bromide and tricyclopentyltin chloride; triphenyltin chloride; $\text{di}(\text{C}_3\text{-C}_7)\text{cycloalkyltin}$ dihalides

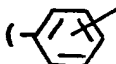

- 13 -

such as dicyclohexyltin dichloride and dicyclopentyltin dichloride; diphenyltin dihalides such as diphenyltin dichloride and diphenyltin bromide; and triphenyltin triflate and tricyclohexyltin triflate.

5 Preferred compounds of formula (4) are those in which the three R's are identical or different and each represents a butyl, cyclohexyl or phenyl group, and tributyltin chloride, triphenyltin chloride, and tricyclohexyltin chloride are especially preferred.

10 The halide used in step (B) is represented by formula (5).



In formula (5), X represents a halogen atom or a tosyl group, Z represents an ethylene group, an ethynylene group, a trans-vinylene group, a cis-vinylene group, a phenylene group () or a phenyleneoxa group () and R_A represents a hydrogen atom or a substituted or unsubstituted C₁-C₇ alkyl or alkenyl group.

20 The substituted or unsubstituted C₁-C₇ alkyl or alkenyl group for R_A in formula (5) may be linear or branched, and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, hexyl and heptyl groups.

25 The unsubstituted C₁-C₇ alkenyl group for R_A may be linear or branched, or a group bonded to the carbon atom of the group Z forming a direct double bond, such as =CH₂, or an alkenyl group bonded to the carbon atom of the group Z through a single bond.

30 Examples of the unsubstituted C₁-C₇ alkenyl group include vinyl, 1-propenyl, 1-butenyl, 1-pentenyl, 1-hexenyl, 1-heptenyl, 2-propenyl, 2-butenyl, 2-pentenyl, 2-hexenyl, 2-heptenyl, 3-butenyl, 3-pentenyl, 3-hexenyl, and 3-heptenyl groups. They may be of an E- or Z-type isomeric form.

- 14 -

Examples of the substituent on the substituted C_1-C_7 alkyl group include cycloalkyl groups having 3 to 7 carbon atoms, a vinyl group, alkynyl groups having 2 to 4 carbon atoms, a phenyl group and a phenoxy group (the phenyl and phenoxy groups may further be substituted by fluoro, methyl, trifluoromethyl or trifluoromethoxy), alkoxy groups having 1 to 4 carbon atoms, groups of the formula OR^2 in which R^2 is as defined above, acyloxy groups having 1 to 4 carbon atoms, an oxo group, and alkoxy-carbonyl groups having 1 to 4 carbon atoms in the alkyl moiety.

Examples of the substituent on the substituted C_1-C_7 alkenyl group include alkyl groups having 1 to 4 carbon atoms, cycloalkyl groups having 3 to 7 carbon atoms, alkynyl groups having 2 to 4 carbon atoms, a phenyl group and a phenoxy group (the phenyl and phenoxy groups may further be substituted by fluoro, methyl, trifluoromethyl or trifluoromethoxy), alkoxy groups having 1 to 4 carbon atoms, groups of the formula OR^2 in which R^2 is as defined above, acyloxy groups having 1 to 4 carbon atoms, an oxo group, and alkoxycarbonyl groups having 1 to 4 carbon atoms in the alkyl moiety.

Examples of the above substituents include alkyl groups having 1 to 4 carbon atoms such as methyl, ethyl, propyl and butyl groups; cycloalkyl groups having 3 to 7 carbon atoms such as cyclopentyl and cyclohexyl groups, a vinyl group; alkynyl groups having 2 to 4 carbon atoms such as ethynyl, propargyl, 1-butyne and 1-propyne groups; phenyl, fluorophenyl, tolyl, trifluoromethylphenyl, trifluoromethoxyphenyl, phenoxy, fluorophenoxy, methylphenoxy, trifluoromethylphenoxy and trifluoromethoxyphenoxy groups; alkoxy groups having 1 to 4 carbon atoms such as methoxy, ethoxy, propoxy and butoxy groups; acyloxy groups having 1 to 4 carbon atoms such as acetoxy and propionyloxy groups, an oxo group; and lower alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl and t-butoxycarbonyl

- 15 -

groups. Specific examples of OR^2 as the substituent will be apparent from the examples given hereinabove with respect to formula (1).

Preferred examples of the halide of formula (5) are compounds represented by the following formula



wherein X is as defined in formula (5), R^1 represents a C_1-C_{10} alkyl group, a substituted or unsubstituted phenyl group, a substituted or unsubstituted C_3-C_7 cycloalkyl group, or substituted or unsubstituted phenyl (C_1-C_2)alkyl group, n is an integer of 1 to 9,

and compounds represented by the following formula



wherein X is as defined in the above formula, Z' represents an ethynylene, trans-vinylene, cis-vinylene, phenylene or phenyleneoxa group, and R'_A represents a C_1-C_7 alkenyl group whose position remotest from the group Z' is substituted by a substituent $-COOR^1$ in which R^1 is as defined above.

In formulae (5)-1 and (5)-2, X is a halogen atom, and R^1 is a C_1-C_{10} alkyl group, a substituted or unsubstituted phenyl group, a substituted or unsubstituted C_3-C_7 cycloalkyl group or a substituted or unsubstituted phenyl (C_1-C_2)alkyl group.

The C_1-C_{10} alkyl group may be linear or branched, and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl and decyl groups.

Examples of preferred substituents for the substituted or unsubstituted phenyl group include halogen atoms, a protected hydroxyl group, acyloxy groups having

- 16 -

2 to 7 carbon atoms, C_1-C_4 alkyl groups optionally substituted by halogen atoms, C_1-C_4 alkoxy groups optionally substituted by halogen atoms, a nitrile group and (C_1-C_6) alkoxy-carbonyl groups. The halogen atoms are, for example, fluorine, chlorine and bromine, the first two being particularly preferred. Examples of the C_2-C_7 acyloxy groups are acetoxy, propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, caproyloxy, enanthyloxy and benzoyloxy groups.

10 Examples of the C_1-C_4 alkyl groups optionally substituted by halogen atoms preferably include methyl, ethyl, isopropyl, butyl, chloromethyl, dichloromethyl and trifluoromethyl groups. Examples of the C_1-C_4 alkoxy groups optionally substituted preferably include methoxy, ethoxy, 15 propoxy, butoxy, chloromethoxy, dichloromethoxy and trifluoromethoxy groups. Examples of the (C_1-C_6) alkoxy-carbonyl groups are methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl and hexyloxycarbonyl groups.

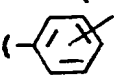

The substituted phenyl group may have 1 to 3
20 substituents exemplified above, preferably one such substituent.

The substituted or unsubstituted C_3-C_7 cycloalkyl groups are, for example, unsubstituted saturated or unsaturated C_3-C_7 , preferably C_5-C_6 , especially preferably 25 C_6 , cycloalkyl groups optionally substituted by the aforesaid substituents, and examples include cyclopropyl, cyclopentyl, cyclohexyl, cyclohexenyl and cycloheptyl groups.

Examples of the substituted or unsubstituted phenyl (C_1-C_2) alkyl groups are benzyl, alpha-phenethyl and 30 beta-phenethyl groups in which the phenyl group is unsubstituted or substituted by the aforesaid substituents.

In formula (5)-1, n is an integer of 1 to 9.

In formula (5)-2, Z' is an ethynylene group

($-C\equiv C-$), a trans-vinylene group ($\text{CH}=\text{CH}$), a cis-vinylene
35 group ($\text{CH}=\text{CH}$), a phenylene group () or a phenylene-oxa group ().

- 17 -

In formula (5)-2, R'_A is a C_1 - C_7 alkenyl group whose position remotest from the group Z' is substituted by a substituent $-COOR^1$ wherein R^1 is as defined hereinabove.

When the C_1 - C_7 alkenyl group is, for example, 1-propenyl ($-C=C-CH_2$) and Z' is an ethynylene group, $-Z'-R'_A$ is $-CH=CH-CH=CH-CH_2-COOR^1$.

In step (B) of the process of this invention, the conjugate added enolate formed in step (A) and being present in the reaction system is reacted with the halide of formula (5), (5)-1 or (5)-2. The reaction is carried out by first adding the organotin compound to the reaction system in which the organocopper compound has been introduced into the 4-substituted-2-cyclopentenone by conjugate addition reaction, and thereafter adding the halide of formula (5) which may be diluted with the aforesaid aprotic organic medium.

It is believed that stoichiometrically, the organotin compound and the enolate reacted in equimolar proportions to form a tin enolate freshly. Usually, the organotin compound is used in an amount of 0.8 to 1.5 moles, especially 1.0 to 1.2 moles, per mole of the 4-substituted-2-cyclopentenone initially used.

The reaction temperature is -100 to 0°C , preferably -78 to -20°C . It is sufficient that the reaction time is usually within 1 hour.

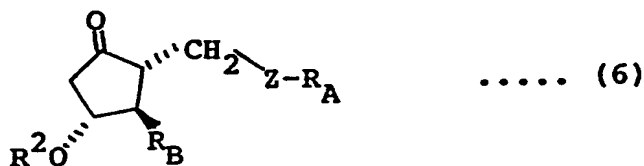
Stoichiometrically, the halide of formula (5) reacts with the enolate formed by conjugate addition-reaction in equimolar proportions. Usually, the halide is used in an amount of 0.8 to 5.0 moles, particularly 1.0 to 2.0 moles, per mole of the 4-substituted-2-cyclopentenone initially used.

The reaction temperature is -100 to 0°C , preferably -78 to -20°C . The reaction time varies depending upon the type of the halide used and the reaction temperature. Usually the reaction is terminated by carrying it out for about 1 hour to 50 hours at a temperature of -78° to -30°C .

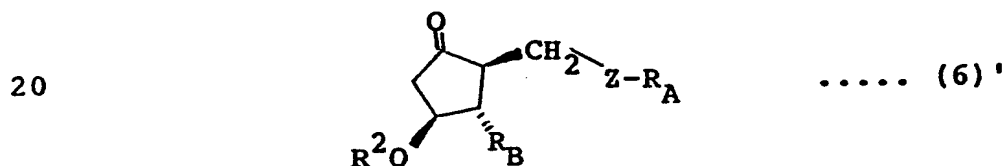
The end point of the reaction may be efficiently determined by monitoring it by, for example, thin-layer chromatography.

Preferably, the alkylation reaction in step (B) with the halide of formula (5) in the process of this invention is carried out in the aforesaid aprotic polar solvent, especially in the presence of hexamethylphosphoric triamide, and this frequently gives good results. After the reaction, the final desired product is isolated and purified by ordinary means such as post-treatment, extraction, washing, chromatography, distillation, or combinations of these.

Thus, according to this invention, there can be produced a 2,3-disubstituted-4-substituted cyclopentanone represented by the following formula

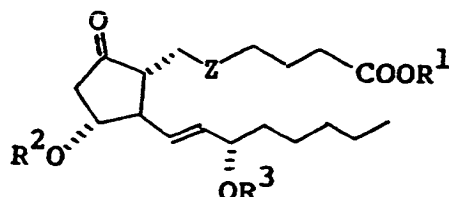


wherein R_A , R_B , R^2 and Z are as defined above, an enantioimorph thereof represented by the following formula



wherein R_A , R_B , R^2 and Z are as defined above, or a mixture of the compounds of formulae (6) and (6)' in arbitrary ratios.

Among the compounds represented by formula (6), those represented by the following formula

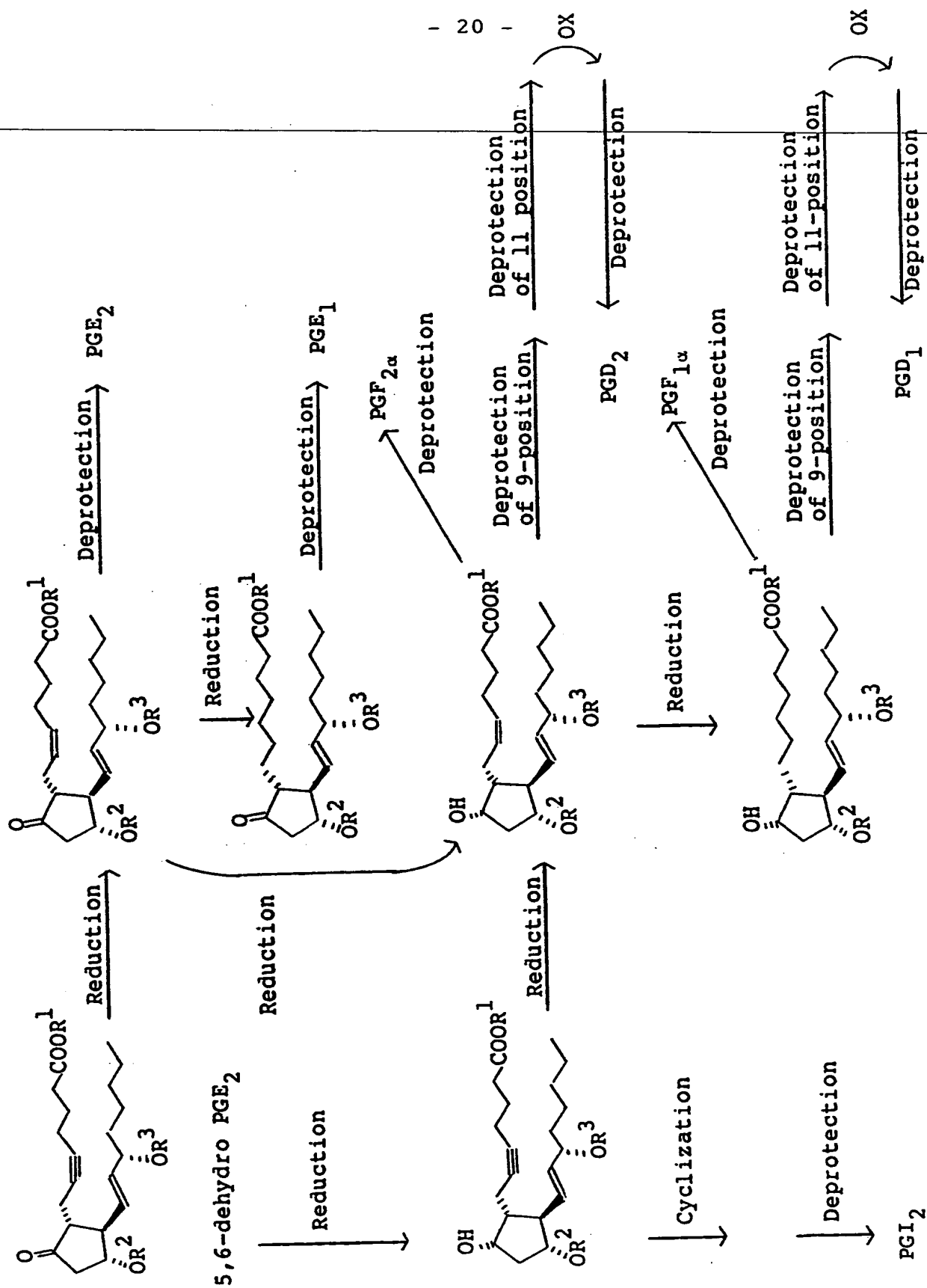


.... (6)-1

wherein R^1 , R^2 , R^3 and Z are as defined above,
are preferred.

Compounds of formula (6)-1 wherein Z is a cis-
5 vinylene group have a PGE_2 skeleton; those in which Z is an
ethynylene group have a 5,6-dehydro PGE_2 skeleton; and
those in which Z is an ethylene group have a PGE_1 skeleton.
The present invention should be fully evaluated as a pro-
cess which can give such useful compounds.

10 To demonstrate the utility of the compounds
produced by the process of this invention, the following
flow chart is given which shows the conversion of a 5,6-
dehydro PGE_2 derivative as a starting material into PGE_2 ,
 E_1 , $F_{2\alpha}$, $F_{1\alpha}$, D_2 , D_1 and I_2 respectively.



- 21 -

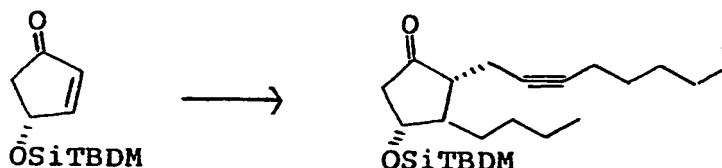
The following Referential Examples 1 to 5 specifically show some of the above conversion reactions. The other conversions reactions were already been reported by some of the present inventors.

One characteristic of the process of this invention is that all the reactions used proceed stereospecifically. Hence, a compound having the steric configuration represented by formula (6) is obtained from a starting material having the steric configuration represented by formula (1), and the enantiomorph of formula (6)' is obtained from the enantiomorph of formula (1)'. Accordingly, from a mixture of these compounds in an arbitrary ratio, a mixture reflecting the mixing ratio is obtained as a final product. Furthermore, since the organolithium compound of formula (2)-A contains an asymmetric carbon, it includes two optical isomers, but any of these optically active isomers or a mixture of them in an arbitrary ratio can be used. Among these, compounds having the steric configuration represented by formula (6)-1 are especially useful stereoisomers because they have the same steric configuration as natural prostaglandins.

The following examples illustrate the present invention more specifically. It should be understood however that the invention is not limited to these specific examples.

EXAMPLE 1

Synthesis of (2R,3R,4R)-3-butyl-4-t-butyl-dimethylsilyloxy-2-(2-octynyl)cyclopentanone:-



TBDM is an abbreviation for t-butyl-dimethyl.

(i) Cuprous iodide (99.1 mg; 0.52 mmole) was weighed into a 30 ml reaction tube purged with argon, and the

- 22 -

inside of the tube was dried under reduced pressure. Then, the reaction tube was again purged with argon. Dry tetrahydrofuran (2 ml) and tributylphosphine (0.337 ml; 1.35 mmole) were introduced into the reaction tube, and stirred at 20°C with stirring to form a uniform solution. The solution was cooled to -78°C, and n-butyllithium (1.60 M, 0.325 ml, 0.52 mmole) was added, and the mixture was stirred at -78°C for 10 minutes. Then, a solution of (R)-4-t-butyltrimethylsiloxy-2-cyclopentenone (100 mg, 0.471 mmole) in tetrahydrofuran (2 ml) was added dropwise at -78°C over 10 minutes. The mixture was stirred at -78°C for 10 minutes. Then, hexamethylphosphoric triamide (1 ml) was added, and the mixture was stirred for 40 minutes at -78°C. Tributyltin chloride (0.14 ml, 0.520 mmole) was added, and the temperature was raised to -40°C. A solution of 1-iodo-2-octyne (184 mg, 0.78 mmole) in tetrahydrofuran (1 ml) was added, and the mixture was stirred for 2 hours. Ether (5 ml) was added to the reaction mixture, and the mixture was successively washed with a saturated aqueous solution of ammonium chloride (5 ml), a saturated aqueous potassium thiocyanate solution (5 ml) and a saturated aqueous sodium chloride solution (5 ml). The separated organic layer was dried over anhydrous sodium sulfate. The dried product was filtered and concentrated under reduced pressure. The resulting crude product was separated by silica gel column chromatography (Merck 7734, 6% water, 20 g; hexane:ethyl acetate=30:1) to give (2R,3R,4R)-3-butyl-4-t-butyltrimethylsiloxy-2-(2-octynyl)cyclopentanone (88.1 mg, 0.233 mmole, 49%).

TLC: R_f=0.39 (hexane:ethyl acetate=10:1)

IR (liquid film):

1750, 1450, 1247, 1098, 834 and 771 cm⁻¹.

NMR (CDCl₃) δ:

0.05 and 0.09 (each s, 6, SiCH₃ x 2),

0.89 (s, 15, SiC(CH₃)₃, CH₃ x 2),

1.1-1.7 (m, 12, CH₂ x 6),

- 23 -

1.8-2.4 (m, 5, $\text{CH}_2\text{C}\equiv\text{C} \times 2$, $\text{CH} \times 1$),
 2.4-2.8 (m, 3, $\text{CH}_2\text{CO} \times 2$, CHCO),
 4.05 (dd, 1, $J=13.0$ and 6.4Hz , CHOSi).

^{13}C NMR (CDCl_3) δ :

-4.9, -4.5, 13.9 (for 2), 18.6, 19.1, 22.1,
 22.9, 25.7 (for 4), 28.7, 29.0, 31.0, 31.7,
 47.7, 48.6, 52.5, 73.3, 77.0, 81.9, 215.4.

MS (74 eV; m/e):

378 (M^+), 321 ($\text{M}^+ - \text{C}_4\text{H}_9$).

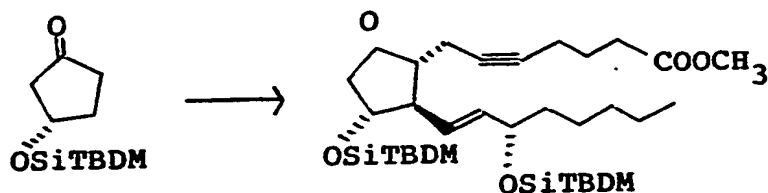
- 10 (ii) Cuprous iodide (198 mg; 1.04 mmole) was weighed
 into a 150 ml reaction tube purged with argon, and the
 inside of the tube was dried under reduced pressure. Then,
 the reaction tube was again purged with argon. Dry tetra-
 15 hydrofuran (10 ml) and tributylphosphine (0.673 ml; 2.70
 mmole) were introduced into the reaction tube, and stirred
 at 19°C with stirring to form a uniform solution. The
 solution was cooled to -78°C , and n-butyllithium (1.60 M,
 0.647 ml, 1.04 mmole) was added, and the mixture was
 stirred at -78°C for 10 minutes. Then, a solution of
 20 (R)-4-t-butyltrimethylsiloxy-2-cyclopentenone (200 mg, 0.942
 mmole) in tetrahydrofuran (15 ml) was added dropwise at
 -78°C over 0.8 hours using a syringe drive. The mixture
 was stirred at -78°C for 10 minutes. Then, hexamethyl-
 phosphoric triamide (2 ml) was added, and the mixture was
 25 stirred for 40 minutes at -78°C . Tributyltin chloride
 (0.28 ml, 1.04 mmole) was added, and the temperature was
 raised to -30°C . A solution of 1-bromo-2-octyne (197 mg,
 1.04 mmole) in tetrahydrofuran (2 ml) was added, and the
 mixture was stirred for 17.5 hours. Ether (10 ml) was
 30 added to the reaction mixture, and the mixture was suc-
 cessively washed with a saturated aqueous ammonium chloride
 solution (10 ml), a saturated aqueous potassium thiocyanate
 solution (10 ml) and a saturated aqueous sodium chloride
 solution (10 ml). The separated organic layer was dried
 35 over anhydrous sodium sulfate. The dried product was

- 24 -

filtered and concentrated under reduced pressure. The resulting crude product was separated by silica gel column chromatography (Merck 7734, 6% water, 20 g; hexane:ethyl acetate=30:1) to give (2R,3R,4R)-3-butyl-4-t-butyldimethyl-
 5 siloxy-2-(2-octynyl)cyclopentanone (58.8 mg, 0.155 mmole, 16%) which coincided with the product obtained in (i) above.

EXAMPLE 2

10 Synthesis of 11,15-bis(t-butyldimethylsilyl)-5,6-dehydroprostaglandin E₂ methyl ester:-



(i) A solution of (E,3S)-3-t-butyldimethylsiloxy-1-iodo-1-octene (354 mg, 0.961 mmole) in dry ether (5 ml) was put in a 150 ml reaction tube purged with argon, and cooled to -95°C. Then, t-butyllithium (1.77 M, 1.09 ml, 1.92
 15 mmoles) was added dropwise and the mixture was stirred for 3 hours at -95 to -78°C.

Separately, cuprous iodide (183 mg, 0.961 mmole) of cupric iodide was weighed into a 30 ml eggplant-shaped
 20 flask. The inside of the tube was dried under reduced pressure and again purged with argon. Tetrahydrofuran (4 ml) and tributylphosphine (0.62 ml, 2.50 mmoles) were added, and the mixture was stirred at 21°C to form a uniform solution. The uniform solution was added at a time to
 25 the above prepared alkenyl lithium solution under argon pressure using a stainless steel tube. The mixture was stirred at -78°C for 5 minutes. Then, a solution of (R)-4-t-butyldimethylsiloxy-2-cyclopentenone (200 mg, 0.942 mmole) in tetrahydrofuran (15 ml) was added dropwise over
 30 1 hour at -78°C using a syringe drive. The mixture was stirred at -78°C for 1 hour. Thereafter, hexamethylphosphoric triamide (2 ml) was added, and the mixture was

- 25 -

stirred at -78°C for 1 hour. Then, tributyltin chloride (0.26 ml, 0.961 mmole) was added, and the temperature was raised to -45°C . A solution of 1-iodo-6-methoxycarbonyl-2-hexyne (276 mg, 1.04 millimoles) in tetrahydrofuran (2 ml) was added, and the mixture was stirred for 1 hour. Ether (20 ml) was added to the reaction mixture, and the mixture was successively washed with a saturated aqueous solution of ammonium chloride (30 ml), a saturated aqueous solution of potassium thiocyanate (30 ml) and a saturated aqueous solution of sodium chloride (30 ml). The separated organic layer was dried over anhydrous sodium sulfate. The dried product was filtered and concentrated under reduced pressure. The resulting crude product was separated by silica gel column chromatography (Merck 7734, 6% water, 40 g; hexane:ethyl acetate=40:1) to give 11,15-bis(*t*-butyldimethylsilyl)-5,6-dehydroprostaglandin E_2 methyl ester (105.6 mg, 0.178 mmole, 19%).

TLC: $R_f=0.50$ (ethyl acetate:hexane=1:5)

IR (liquid film):

1746, 1246, 827 and 767 cm^{-1} .

^1H NMR (CDCl_3 - CCl_4 =1:1) δ :

0.04 and 0.06 (each s, 12, $\text{SiCH}_3 \times 2$),
 0.89 (s, 18, $\text{SiC}(\text{CH}_3)_3 \times 2$),
 0.92 (t, 1, $J=6.5\text{Hz}$, CH_3),
 1.1-1.5 (m, 8, $\text{CH}_2 \times 4$),
 1.7-2.9 (m, 12, $\text{CH}_2\text{CO} \times 2$, $\text{CH}_2\text{C}\equiv\text{C} \times 2$, $\text{CH} \times 2$ and CH_2),
 3.65 (s, 3, OCH_3), 4.05 (m, 2, $\text{CHOSi} \times 2$),
 5.4-5.7 (m, 2, vinyl).

^{13}C NMR (CDCl_3) δ :

-4.7, -4.5, (for 2), -4.2, 13.6, 14.0, 16.9,
 18.0, 18.2, 22.6, 24.2, 25.0, 25.8 (for 3), 25.9,
 (for 3), 31.9, 32.7, 38.6, 47.7, 51.4, 51.9,
 52.9, 72.7, 73.1, 77.3, 80.8, 128.2, 136.8,
 173.4, 213.4.

$[\alpha]_D^{21}$: -13.9° ($\underline{\text{C}}$ 1.59, CH_3OH).

- 26 -

(ii) A solution of (E,3S)-3-t-butyldimethylsiloxy-1-iodo-1-octene (354 mg, 0.961 mmole) in dry ether (5 ml) was added to a 150 ml argon-purged reaction tube, and cooled to 95°C. Then, t-butyllithium (1.77 M, 1.09 ml, 1.92 mmoles) was added dropwise, and the mixture was stirred for 3 hours at -95 to -78°C.

Separately, cuprous iodide (183 mg, 0.961 mmole) was weighed into a 30 ml eggplant-shaped flask. The inside of the tube was dried under reduced pressure and again purged with argon. Tetrahydrofuran (4 ml) and tributylphosphine (0.62 ml, 2.50 mmoles) were added and stirred to form a uniform solution.

The uniform solution was added at a time to the alkenyllithium solution prepared above under argon pressure using a stainless steel tube. The stainless steel tube was washed with tetrahydrofuran (2 ml), and the washing was also added dropwise. The mixture was stirred at -78°C for 5 minutes. Then, a solution of (R)-4-t-butyldimethylsiloxy-2-cyclopentenone (200 mg, 0.942 mmole) in tetrahydrofuran (10 ml) was added dropwise over 30 minutes at -78°C using a syringe drive. The mixture was stirred at -78°C for 10 minutes. Thereafter, tributyltin chloride (0.26 ml, 0.961 mmole) was added, and the mixture was stirred at -78°C for 1 hour. A solution of 1-iodo-6-methoxycarbonyl-2-hexyne (276 mg, 1.04 mmoles) in tetrahydrofuran (2 ml) was added, and the mixture was stirred for 20 minutes. Hexamethylphosphoric triamide (0.9 ml) was added, and the mixture was stirred at -78°C for 15 minutes. The temperature was then elevated to -45°C, and the mixture was stirred for 30 minutes. Hexamethylphosphoric triamide (0.9 ml) was added, and the mixture was stirred for 1.5 hours. A saturated aqueous ammonium chloride solution (30 ml) was added to the reaction mixture, and the mixture was vigorously shaken. The mixture was separated into an organic layer and an aqueous layer. The organic layer was successively washed with a saturated aqueous solution of

- 27 -

potassium thiocyanate (30 ml), and a saturated aqueous sodium chloride solution (30 ml), and then dried over anhydrous sodium sulfate. The dried product was filtered and concentrated under reduced pressure. The crude product
5 obtained was separated by silica gel column chromatography (Merck 7734, 6% water, 40 g, ethyl acetate:hexane=1:40) to give 11,15-bis(t-butyldimethylsilyl)-5,6-dehydroprosta-
glandin E₂ methyl ester (173.9 mg, 0.293 mmole, 31%). The various spectral data of this product agreed with those
10 given in section (i) above.

(iii) (E)-1-iodo-3-t-butyloxy-1-octene (593.1 mg, 1.61×10^{-3} mole) and dry ether (6 ml) were taken into a 150 ml argon-purged reaction tube. Then, t-butyllithium (1.72 ml, 3.22×10^{-3} mole) was added by using a syringe,
15 and the mixture was stirred at -95 to -78°C for 3 hours. Separately, cuprous iodide (306.6 mg, 1.61×10^{-3} mole) was taken into a 30 ml eggplant-shaped flask. The inside of the tube was dried under heat and reduced pressure, and then purged with argon. Dry tetrahydrofuran (6 ml) and
20 tributylphosphine (1.04 ml, 4.19×10^{-3} mole) were added, and the mixture was stirred at 23°C to form a uniform solution. The solution was cooled to -78°C, and added at a time to the above prepared vinyl lithium solution under argon pressure by means of a stainless steel tube. The
25 mixture was stirred at -78°C for 10 minutes. A solution of 4-t-butyldimethylsiloxy-2-cyclopentenone (325.6 mg, 153×10^{-3} mole) in THF (12 ml) was added dropwise over 1 hour. The reaction tube was washed with 1 ml of THF, and the mixture was further stirred for 10 minutes. HMPA (1.5 ml)
30 was added, and the mixture was stirred for 30 minutes. Thereafter, a solution of triphenyltin chloride (627.6 mg, 1.61×10^{-3} mole) in 2 ml of THF was added, and after the temperature was elevated to -30°C, a solution of 1-iodo-6-carbomethoxy-2-hexyne (814.2 mg, 3.06×10^{-3} mole) in
35 HMPA was added, and the mixture was stirred at -30°C for 4.5 hours. Subsequently, the mixture was left to stand at

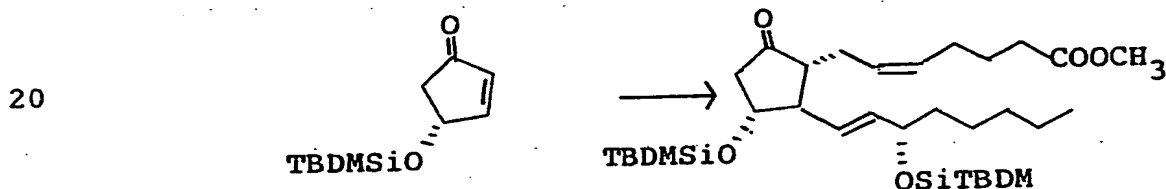
- 28 -

-27°C for 13 hours, and a saturated aqueous ammonium chloride solution (20 ml) was added. The mixture was vigorously shaken to separate it into an organic layer and an aqueous layer. The aqueous layer was extracted with ether (20 ml x 2). The ethereal layers were combined, washed with a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. The dried product was filtered and concentrated under reduced pressure. The resulting crude product was separated by silica gel column chromatography (Merck 7734, 50 g, ethyl acetate:hexane=1:60, 600 ml → 1:20=ethyl acetate:hexane, 200 ml) to give dl-11,15-bis(t-butyldimethylsilyl)-5,6-dehydroprostaglandin E₂ methyl ester (542.1 mg, yield 59.7%).

IR (liquid film):
1746, 1246, 827 and 767 cm⁻¹.

EXAMPLE 3

Synthesis of 11,15-bis(t-butyldimethylsilyl)-prostaglandin E₂ methyl ester:-



(i) A solution of (E, 3S)-3-t-butyldimethylsiloxy-1-iodo-1-octene (354 mg, 0.961 mmole) in dry ether (5 ml) was put in a 150 ml reaction tube purged with argon, and cooled to -95°C. Then, t-butyllithium (1.77 M, 1.09 ml, 1.92 mmol) was added dropwise, and the mixture was stirred for 3 hours at -95 to -78°C. Separately, cuprous iodide (183 mg, 0.961 mmole) was weighed into a 30 ml eggplant-shaped flask. The inside of the tube was dried under reduced pressure and purged again with argon. Tetrahydrofuran (4 ml) and tributylphosphine (0.62 ml, 2.50 mmol) were added, and the mixture was stirred at 29°C to

- 29 -

form a uniform solution. The uniform solution was added at once under argon pressure to the alkenyllithium solution prepared above by means of a stainless steel tube. The mixture was stirred at -78°C for 5 minutes. Then, a solution of (R)-4-t-butyldimethylsiloxy-2-cyclopentenone (200 mg, 0.942 mmole) in tetrahydrofuran (10 ml) was added dropwise over 30 minutes by means of a syringe drive. The mixture was then stirred at -78°C for 10 minutes. Thereafter, tributyltin chloride (0.26 ml, 0.961 mmole) was added, and the mixture was stirred at -78°C for 30 minutes. Hexamethylphosphoric triamide (1.8 ml) was added, and a solution of (Z)-1-iodo-6-methoxycarbonyl-2-hexene (279 mg, 1.04 mmoles) in tetrahydrofuran (2 ml) was added, and the temperature was raised to -45°C . The mixture was stirred for 2 hours. A saturated aqueous ammonium chloride solution (40 ml) was added to the reaction mixture, and the mixture was vigorously shaken to separate it into an organic layer and an aqueous layer. The organic layer was successively washed with a saturated aqueous potassium thiocyanate solution (40 ml) and a saturated aqueous sodium chloride solution (40 ml), and dried over anhydrous sodium sulfate. The dried product was filtered and concentrated under reduced pressure. The crude product was separated by silica gel column chromatography (Merck 7734, 40 g, ethyl acetate:hexane=1:20 to give 11,15-bis(t-butyldimethylsilyl)prostaglandin E_2 methyl ester (142.5 mg, 0.239 mmole, 25%).

TLC: $\text{Rf}=0.58$ (ethyl acetate:hexane=1:5)

IR (liquid film):

1743, 1243, 1000, 964, 927, 828 and 768 cm^{-1} .

^1H NMR (CDCl_3) δ :

0.03 and 0.06 (each s, 12, $\text{SiCH}_3 \times 2$),
0.8-1.0 (m, 21, $\text{C-CH}_3 \times 7$),
1.2-1.5 (m, 8, $\text{CH}_2 \times 4$),
1.6-2.9 (m, 12, $\text{CH}_2\text{CO} \times 2$, $\text{CH}_2\text{C}=\times 2$, $\text{CH} \times 2$
and CH_2),

- 30 -

3.67 (s, 3, OCH_3), 4.06 (m, 2, $\text{CHOSi} \times 2$),

5.37 (m, 2, vinyl), 5.54 (m, 2, vinyl).

 $[\alpha]_D^{21}$: -52.7° (c 1.28, CH_3OH).

(ii) (E)-1-iodo-3-t-butyldimethylsiloxy-1-octene
5 (593.1 mg, 1.61×10^{-3} mole) and 6 ml of dry ether were
taken into a 150 ml argon-purged reaction tube, cooled to
 -95°C , and kept stirred. t-Butyllithium (1.72 ml, $3.22 \times$
 10^{-3} mole) was added by means of a syringe, and the mixture
was stirred at -95 to -78°C for 3 hours. Separately,
10 cuprous iodide (306.6 mg, 1.61×10^{-3} mole) was taken into
a 30 g eggplant-shaped flask. The inside of the tube was
dried under heat and reduced pressure, and then purged with
argon. Dry THF (6 ml) and tributylphosphine (1.04 ml, 4.19
 $\times 10^{-3}$ mole) were added, and the mixture was stirred at
15 25°C to form a uniform solution. The uniform solution was
cooled to -78°C , and added at a time under argon pressure
by means of a stainless steel tube to the vinylolithium
solution prepared above. The mixture was stirred at -78°C
for 10 minutes. HMPA (1.5 ml) was added, and the mixture
20 was stirred for 30 minutes. Triphenyltin chloride (627.6
ml, 1.61×10^{-3} mole) in THF (2 ml) was added. The tem-
perature was elevated to -30°C , and a solution of (Z)-
1-iodo-6-carbomethoxy-2-hexene (1.231 g, 4.59×10^{-3} mole)
in HMPA was added. The mixture was stirred at -30°C for
25 3 hours. Subsequently, the reaction mixture was left to
stand at -27°C for 97.9 hours, and then a saturated aqueous
ammonium chloride solution (20 ml) was added. The mixture
was shaken vigorously to separate it into an organic layer
and an aqueous layer. The organic layer was washed with a
30 saturated aqueous sodium chloride solution and dried over
anhydrous sodium sulfate. The dried product was filtered
and concentrated under reduced pressure. The crude product
was subjected to short chromatography (Merck 7734, 5 g,
ethyl acetate:hexane=1:5) to remove highly polar substances
35 (tributylphosphine and triphenyltin chloride). The product

- 31 -

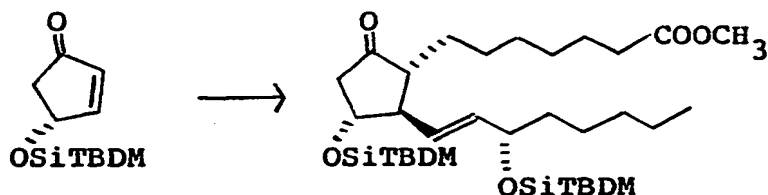
was purified by silica gel column chromatography (Merck 7734, 50 g, 1:60=ethyl acetate:hexane, 780 ml → 1:20=ethyl acetate:hexane, 600 ml) to give dl-11,15-bis(t-butyldimethylsilyl)prostaglandin E₂ methyl ester (647 mg, yield 71%).

IR (liquid film):

1743, 1243, 1000, 964, 927, 828, and 768 cm⁻¹).

EXAMPLE 4

Synthesis of 11,15-bis(t-butyldimethylsilyl)-prostaglandin E₁ methyl ester:-



(E, 3S)-3-t-butyldimethylsilyloxy-1-iodooctene (607.8 mg; 1.65×10^{-3} mole) and 6 ml of dry ether were weighed into a 150 ml. argon-purged reaction tube, cooled to -95°C, and stirred. t-Butyllithium (1.92 M, 1.72 ml, 3.30×10^{-3} mole) was added to the mixture by means of a syringe, and the mixture was stirred at -95 to -78°C for 3 hours.

Separately, a 30 ml eggplant-shaped flask was provided, and cuprous iodide (314.2 mg; 1.65×10^{-3} mole) was weighed into it. The reaction mixture in the flask was dried by heating under reduced pressure, and then the reaction system was purged with argon. Dry THF (6 ml) and tributylphosphine (1.07 ml; 4.29×10^{-6} mole) were added, and the mixture was stirred at room temperature to form a uniform solution. The solution was cooled to -78°C and added at a time to the above prepared vinyl lithium solution by means of a stainless steel tube under argon pressure. After stirring at -78°C for 10 minutes, a THF solution (12 ml) of (R)-4-t-butyldimethylsilyloxy-2-cyclopentenone (318.5 mg, 1.50×10^{-3} mole) was added dropwise over

- 32 -

1 hour. The flask was further washed with 1 ml of THF, and the washing was added. The reaction mixture was stirred for 10 minutes. To the reaction mixture was added 1.5 ml of hexamethylphosphoric triamide (HMPA), and the mixture was stirred for 30 minutes. Then, a THF solution (2 ml) of triphenyltin chloride (643.2 mg; 1.65×10^{-3} mole) was added. The reaction solution was heated to -20°C , and an HMPA solution (2.87 ml) of methyl 6-iodohexanoate (2.0882 mg; 7.73×10^{-3} mole) was added. The mixture was stirred at -20°C for 16 hours. After the reaction, 20 ml of a saturated aqueous solution of ammonium chloride was added, and the mixture was well shaken to separate it into an organic layer and an aqueous layer. The aqueous layer was extracted with ether (2 x 20 ml). The organic layers were combined and washed with a saturated aqueous sodium chloride solution (20 ml), and dried over anhydrous sodium sulfate. The desiccant was removed by filtration, and the residue was concentrated under reduced pressure. The concentrate was chromatographed on a silica gel column (Merck 7734, 5 g; 1:5=ethyl acetate:hexane). The resulting crude concentrated product was chromatographed on a column of silica gel (Merck 7734, 50 g; ethyl acetate:hexane=1:60, 900 ml \rightarrow ethyl acetate:hexane=1:20, 600 ml) to give 178.7 mg (20%) of 11,15-bis(1-butyldimethylsilyl)prostagalndin E₁ methyl ester.

TLC: Rf=0.52 (ethyl acetate:hexane=1:5)

¹H NMR (CDCl₃) δ :

5.6-5.4 (m, 2H), 4.2-3.8 (m, 2H), 3.66 (s, 3H),

2.64 (dd, 1H, J=7.2, 18.4Hz), 2.4-1.8 (m, 4H),

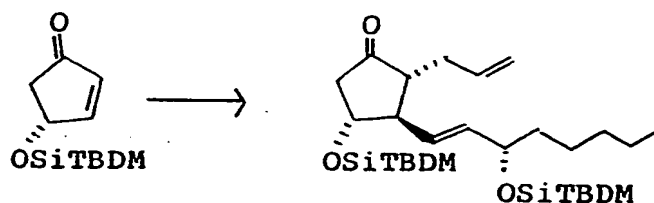
1.7-1.0 (m), 1.0-0.8 (m, 21H), 0.1-0.0 (m).

IR (neat): 1750 cm⁻¹.

EXAMPLE 5

Synthesis of (2R,3R,4R)-2-allyl-4-t-butyldi-methylsilyloxy-3-[(E,3S)-3-t-butyldimethylsilyl-oxy-1-1-octenyl]cyclopentanone:-

- 33 -



The procedure of Example 3 was repeated except that allyl iodide was used instead of (Z)-1-iodo-6-methoxycarbonyl-2-hexene. (2R,3R,4R)-2-allyl-4-t-butyldimethylsilyloxy-3-[(E,3S)-3-t-butyldimethylsilyl-oxy-1-octenyl]-cyclopentanone was obtained in a yield of 71%.

^1H NMR (CDCl_3) δ :

0.07 (12H, s), 0.86 (21H, s), 1.1-1.5 (8H, m),
1.6-2.8 (6H, m), 3.8-4.3 (2H, m),
4.75-5.60 (5H, m).

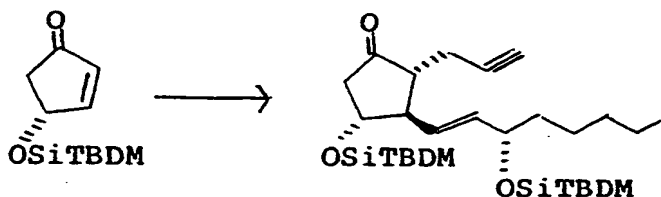
IR (liquid film):

3100, 1745, 1255, 1110, 965, 910, 875, 835,
810 and 770 cm^{-1} .

MS (m/e): 494, 479, 437 and 379.

EXAMPLE 6

Synthesis of (2R,3R,4R)-4-t-butyldimethylsilyloxy-3-[(E,3E)-3-t-butyldimethylsilyloxy-1-octenyl]-2-(2-propynyl)cyclopentanone:-



20

The procedure of Example 2 was repeated except that propargyl iodide was used instead of 1-iodo-6-methoxycarbonyl-2-hexyne. (2R,3R,4R)-4-t-butyldimethylsilyloxy-3-[(E,3S)-3-t-butyldimethylsilyloxy-1-octenyl]-2-(2-propargyl)cyclopentanone was obtained in a yield of 65%.

- 34 -

¹H NMR (CDCl₃) δ:

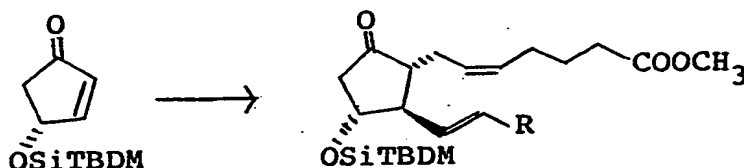
0.06 (12H, s), 0.87 (21H), 1.0-1.7 (8H, m),
 1.8-3.0 (7H, m), 3.7-4.2 (2H, m),
 5.3-5.6 (2H, m).

5 IR (liquid film):

3330, 1755, 1255, 1155, 1120, 1090, 1005, 965,
 880, 835 and 775 cm⁻¹.

EXAMPLES 7-16

10 Syntheses of 11,15-bis(t-butyldimethylsilyloxy)-
 prostaglandin E₂ methyl esters:-



The following compounds were synthesized by the
 same procedure as in Example 3 (yields 19-67%).

15 Example 7: 11,15-bis(t-butyldimethylsilyl)-
 17(R),20-dimethylprostaglandin E₂ methyl ester

Example 8: 11,15-bis(t-butyldimethylsilyl)-
 17(S),20-dimethylprostaglandin E₂ methyl ester

20 Example 9: 11,15-bis(t-butyldimethylsilyl)-
 16,17,18,19,20-pentanor-15-cyclopentylprostaglandin E₂
 methyl ester

Example 10: 11,15-bis(t-butyldimethylsilyl)-
 16,17,18,19,20-pentanor-15-cyclohexylprostaglandin E₂
 methyl ester

25 Example 11: 11,15-bis(t-butyldimethylsilyl)-
 15-methylprostaglandin E₂ methyl ester

Example 12: 11,15-bis(t-butyldimethylsilyl)-
 16,16-dimethylprostaglandin E₂ methyl ester

Example 13: 11,15-bis(t-butyldimethylsilyl)-
 20-isopropylidene-17-methylprostaglandin E₂ methyl ester

30 Example 14: 11,15-bis(t-butyldimethylsilyl)-
 18,18,19,19-tetrahydro-16-methylprostaglandin E₂ methyl
 ester

- 35 -

Example 15: 11,15-bis(t-butyldimethylsilyl)-
18,19,20-trinor-17-phenylprostaglandin E₂ methyl ester

Example 16: 11-(t-butyldimethylsilyl)-15-
5 deoxy-16-trimethylsilyloxy-16-vinylprostaglandin E₂ methyl ester

The characteristic spectral data of the compounds obtained in Examples 7 to 16 are listed in Table 1.

EXAMPLES 17-18

10 Synthesis of 11,15-bis(t-butyldimethylsilyloxy)-prostaglandin E₂ analogues:-

The following compounds were synthesized in the same way as in Example 1 and Examples 7-16 (yields 35-49%).

Example 17: 11,15-bis(t-butyldimethylsilyl)-
2,3-dehydro-17,18,19,20-tetranor-16-[3-(alpha,alpha,alpha-
15 trifluoromethyl)phenoxy]prostaglandin E₂ methyl ester

Example 18: 11,15-bis(t-butyldimethylsilyl)-
4,5,6-trinor-3,7-inter-m-phenylene-3-oxaprostaglandin E₂
methyl ester

20 The characteristic spectral data of the compounds obtained in Examples 17 and 18 are shown in Table 1.

EXAMPLES 19-20

Synthesis of prostaglandin E₁ methyl ester analogues:-

25 The following compounds were synthesized by the same procedure as in Example 4 (yields 17-32%).

Example 19: 11-(t-butyldimethylsilyl)-15-deoxy-
16-methyl-16-trimethylsilyloxyprostaglandin E₁ methyl ester

Example 20: (4Z)-Δ⁴-11-(t-butyldimethylsilyl)-
15-deoxy-16-methyl-16-trimethylsilyloxyprostaglandin E₁
30 methyl ester

The characteristic spectral data of the compounds obtained in Examples 19 and 20 are shown in Table 1.

- 36 -
Table 1

Ex- ample	^1H NMR (CDCl_3) δ	IR (liquid film) cm^{-1}	MS
7	0.03 and 0.06 (12H, s), 0.8-1.0 (24H, m), 1.2-1.5 (9H, m), 1.6-2.9 (12H, m), 3.67 (3H, s), 3.9-4.2 (2H, m), 5.25-5.5 (2H, m), 5.5-5.65 (2H, m).	1745, 1245, 1000, 965, 930, 830, 770.	565 (M-57).
8	0.03 and 0.06 (12H, s), 0.8-1.0 (24H, m), 1.2-1.5 (9H, m), 1.6-2.9 (12H, m), 3.67 (3H, s), 3.9-4.2 (2H, m), 5.25-5.5 (2H, m), 5.5-5.65 (2H, m).	1745, 1245, 1000, 965, 930, 830, 770.	565 (M-57).
9	0.06 (12H), 0.8-1.0 (18H, s), 1.1-1.5 (9H, m), 1.6-2.9 (12H, m), 3.67 (3H, s), 3.9-4.2 (2H, m), 5.25-5.65 (4H, m).	1745, 1245, 1000, 965, 930, 830, 770.	535 (M-57).
10	0.06 (12H), 0.8-1.0 (18H, s), 1.1-1.5 (11H, m), 1.6-2.9 (12H, m), 3.67 (3H, s), 3.9-4.2 (2H, m), 5.25-5.65 (4H, m).	1745, 1245, 1000, 965, 930, 830, 770.	549 (M-57).
11	0.03 and 0.06 (12H, s), 0.90 (21H), 1.23 (3H, s), 0.9-1.6 (10H, m), 1.6-2.7 (10H, m), 3.65 (3H, s), 4.1 (1H, m), 5.5 (4H, m).	1745, 1250, 1155, 1095, 1005, 835, 770.	609 (M+1). 551 (M-57).
12	0.06 (12H), 0.87 (21H), 1.14 (6H, s), 1.0-2.8 (18H, m), 3.60 (3H, s), 3.8-4.2 (2H, m), 5.2-5.6 (4H, m).	1745, 1245, 1000, 965, 930, 830, 770.	565 (M-57).
13	0.06 (12H), 0.87 (21H), 1.5-1.8 (6H, d), 1.0-2.8 (19H, m), 3.63 (3H, s), 3.8-4.2 (2H, m), 4.8-5.6 (4H, m), 6.5-7.2 (1H, m).	1745, 1255, 1000, 965, 935, 835, 770.	591 (M-57).

- to be continued -

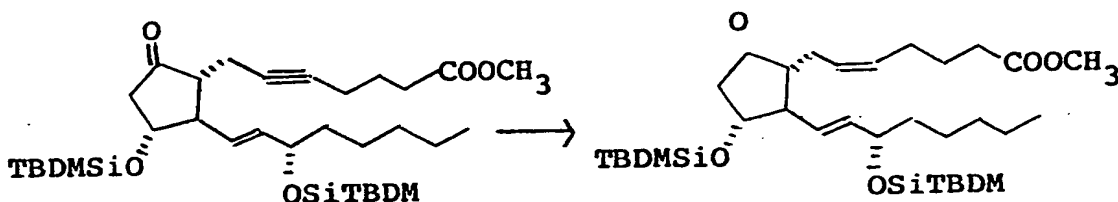
Table 1 (continued)

Ex-ample	^1H NMR (CDCl_3) δ	IR (liquid film) cm^{-1}	MS
14	0.06 (12H), 0.87 (24H, m), 1.0-2.9 (19H, m), 3.65 (3H, s), 3.9-4.2 (2H, m), 5.25-5.6 (4H, m).	2250, 1745, 1255, 1000, 970, 935, 830, 770.	547 (M-57).
15	0.06 (12H), 0.87 (18H, s), 1.0-2.9 (16H, m), 3.63 (3H, s), 3.9-4.2 (2H, m), 5.3-5.6 (4H, m), 7.3 (5H, s).	3030, 1745, 1600, 1255, 1005, 965, 935, 830, 770.	571 (M-57).
16	0.05 (6H, s), 0.90 (9H, s), 0.87 (12H, s+t), 1.1-1.9 (16H, m), 2.1-2.6 (8H, m), 3.65 (3H, s), 4.2-4.5 (1H, m), 4.7-5.6 (7H, m).	3080, 1745, 1250, 1005, 965, 930, 830, 770.	563 (M-57).
17	0.06 (12H), 0.87 (21H, s+t), 1.0-2.9 (12H, m), 2.6 (2H, d), 3.73 (3H, s), 4.2-4.5 (2H, m), 4.67 (2H, s), 6.7-7.4 (4H, m).	3050, 1745, 1600, 1585, 1255, 1090, 1055, 965, 835, 775.	632 (M ⁺). 575 (M-57).
18	0.06 (12H), 0.85 (18H, s), 1.1-3.0 (10H, m), 3.63 (3H, s), 3.93 (2H, d), 3.9-4.3 (2H, m), 5.2-5.7 (4H, m), 6.7-7.6 (6H, m).	3050, 1745, 1725, 1600, 1315, 1255, 1005, 965, 930, 835, 770.	696 (M ⁺). 639 (M-57).
19	0.05 (6H, s), 0.10 (9H, s), 0.86 (12H, s+t), 1.15 (3H, s), 1.1-1.9 (16H, m), 2.1-2.6 (8H, m), 3.64 (3H, s), 4.2-4.5 (1H, m), 5.2-5.8 (2H, m).	1740, 1250, 1170, 1100, 1060, 970, 860, 835, 775, 750.	512. 395. 173. 58.
20	0.05 (6H, s), 0.09 (9H, s), 0.85 (12H, s+t), 1.15 (3H, s), 1.0-2.7 (22H, m), 3.63 (3H, s), 4.2-4.5 (1H, m), 5.1-5.8 (4H, m).	1740, 1255, 1170, 1100, 1060, 970, 860, 835, 770, 750.	509 (M-57).

- 38 -

REFERENTIAL EXAMPLE 1

Synthesis of 11,15-bis(t-butyldimethylsilyl)-
prostaglandin E₂ methyl ester:-



5 11,15-bis(t-butyldimethylsilyl)-5,6-dehydro-
prostaglandin E₂ methyl ester (48.2 mg; 0.081 mmole) and
synthetic quinoline (25 mg) were dissolved in benzene (2.5
ml), and cyclohexane (2.5 ml) and then 5% Pd-BASO₄ (25 mg)
were added. The mixture was stirred at 25°C for 3 hours in
10 an atmosphere of hydrogen. Then, synthetic quinoline (50
mg) and 5% PdBaSO₄ (50 mg) were additionally supplied, and
the mixture was stirred at 40°C for 4.5 hours. The cata-
lyst was removed by filtration, and the filtrate was washed
with ethyl acetate. The washings were combined, and con-
15 centrated under reduced pressure.

The concentrate was chromatographed on a silica
gel column (8 g, ether:hexane=1:10). The collected frac-
tions were concentrated under reduced pressure. The re-
sidue was left to stand for 7 hours under reduced pressure
20 (<4 mmHg) created by a vacuum pump to give 11,15-bis(t-
butyldimethylsilyl)prostaglandin E₂ methyl ester (41.8 mg;
87%).

TLC: R_f=0.58 (ethyl acetate:hexane=1:5)

IR (liquid film):

25 1743, 1243, 1000, 964, 927, 828 and 768 cm⁻¹.

¹H NMR (CDCl₃) δ:

0.03 and 0.06 (each s, 12, SiCH₃ x 4),
0.8-1.0 (m, 21, C-CH₃ x 7),
1.2-1.5 (m, 8, CH₂ x 4),
30 1.6-2.9 (m, 12, CH₂CO x 2, CH₂C= x 2, CH x 2
and CH₂),

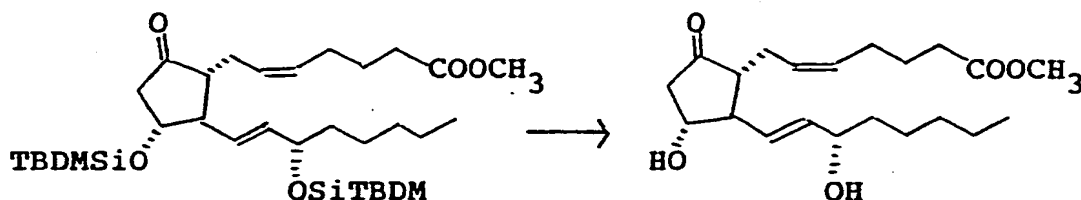
- 39 -

3.67 (s, 3, OCH₃), 4.06 (m, 2, CHOSi x 2),
 5.37 (m, 2, vinyl), 5.54 (m, 2, vinyl).
 $[\alpha]_D^{21}$: -52.7° (C 1.28, CH₃OH).

This compound completely agreed with the 11,15-
 5 protected disilyl compound derived from (-)-PGE₂.

REFERENTIAL EXAMPLE 2

Synthesis of prostaglandin E₂ methyl ester:-



11,15-bis(t-butyldimethylsilyl)prostaglandin E₂
 10 methyl ester (40 mg, 0.067 mmole) was dissolved in an-
 anhydrous acetonitrile (8 ml), and at 0°C, HF-pyridine (0.1
 ml) was added. The mixture was stirred at 24°C for 30
 minutes. HF-pyridine (0.4 ml) was added further, and the
 mixture was stirred for 3 hours, and then poured into a
 15 saturated aqueous sodium bicarbonate solution (20 ml).
 The mixture was extracted with ethyl acetate three times
 (30 ml x 3). The organic layers were combined, dried over
 anhydrous sodium sulfate, and concentrated under reduced
 pressure. Toluene was added to the residue, and the mix-
 20 ture was further concentrated under reduced pressure in
 order to remove pyridine from the residue. The residue was
 left to stand for a while under reduced pressure (<4 mmHg)
 created by a vacuum pump, and then chromatographed on a
 silica gel column [2 g, ethyl acetate:hexane (1:1) → (1:0)
 25 gradient] to give (-)-PGE₂ methyl ester (24.1 mg, 98%).

TLC: R_f=0.29 (ethyl acetate:cyclohexane:THF=6:3:1)

IR (liquid film):

3680-3080, 1744 and 970 cm⁻¹.

¹H NMR (CDCl₃) δ:

30 0.90 (t, 1, J=6.5Hz, CH₃),

- 40 -

1.1-2.9 (m, 20, $\text{CH}_2\text{CO} \times 2$, $\text{CH}_2 \times 5$, $\text{CH}_2\text{C}=\times 2$,
 $\text{CH} \times 2$),

3.08 (br, 1, OH), 3.66 (s, 3, OCH_3),

4.06 (m, 3, $\text{CHO} \times 2$ and OH),

5 5.34 (m, 1, vinyl), 5.70 (m, 1, vinyl).

^{13}C NMR ($\text{CDCl}_3\text{-CCl}_4$) δ :

14.0, 22.6, 24.7, 25.1, 26.6, 31.7, 33.5, 37.3,

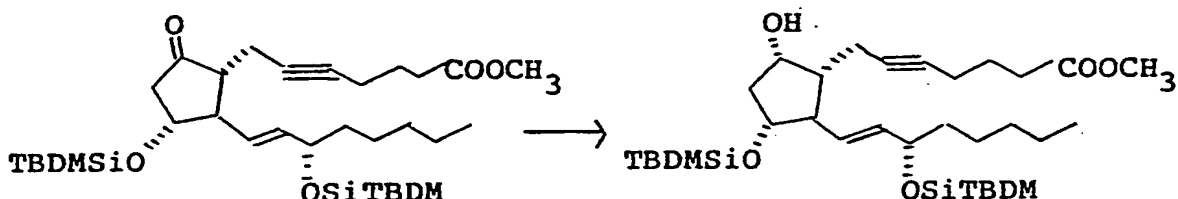
46.1, 51.5, 53.7, 54.5, 72.0, 73.0, 126.6,

130.8, 131.5, 136.8, 174.0, 214.1.

10 $[\alpha]_D^{22}$: -71.7° (c 1.043, CH_3OH).

REFERENTIAL EXAMPLE 3

Synthesis of 11,15-bis(t-butyldimethylsilyl)-
 5,6-prostaglandin $\text{F}_{2\alpha}$ methyl ester:-



15 A toluene solution (1 ml) of 11,15-bis(t-butyl-
 dimethylsilyl)-5,6-dehydroprostaglandin E_2 methyl ester
 (25.5 mg; 0.043 mmole) was added at -78°C to a toluene
 solution (0.192 M; 2.24 ml; 0.43 mmole) of diisobutyl-
 aluminum hydride (1 equivalent)/2,6-di-t-butyl-4-methyl-
 20 phenol (2 equivalents). The mixture was stirred at -78°C
 for 2 hours. The temperature was then elevated, and the
 mixture was stirred at -25 to -20°C for 3 hours. A satu-
 rated aqueous sodium hydrogen tartrate solution (10 ml)
 was added, and the mixture was vigorously shaken. It was
 25 extracted three times with ethyl acetate (20+10+10 ml) at
 room temperature. The organic layers were combined, dried
 over anhydrous sodium sulfate, and concentrated under
 reduced pressure.

30 The residue was chromatographed on a silica gel
 column (5 g, ethyl acetate:hexane=5:1) to give 11,15-bis-
 (t-butyldimethylsilyl)-5,6-dehydroprostaglandin $\text{F}_{2\alpha}$ methyl
 ester (23.5 mg, 92%, a component having low polarity).

- 41 -

TLC: Rf=0.29 (ethyl acetate:hexane=1:5)

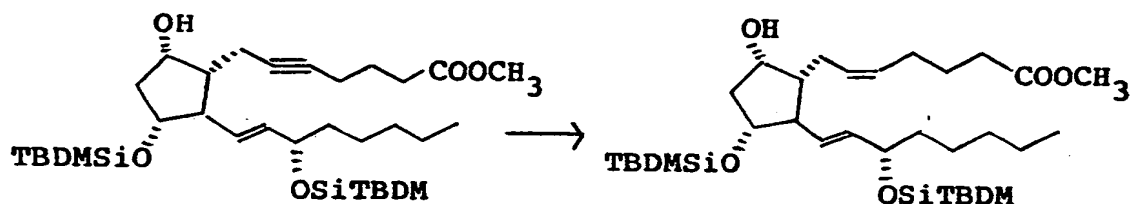
IR (liquid film):

3640-3080, 1745, 1247, 1020, 970, 930, 830 and
770 cm^{-1} .5 ^1H NMR (CDCl_3) δ :0.02 and 0.05 (each s, 12, SiCH_3 x 4),0.7-1.0 (m, 21, C-CH_3 x 7),2.1-3.5 (m, 20, CH_2CO , CH_2 x 6, $\text{CH}_2\text{C=}$ x 2,
and CH x 2),10 3.69 (d, 1, $J=8.3\text{Hz}$, OH), 3.67 (s, 3, OCH_3),4.00 and 4.24 (br, 3, CHO x 3),

5.40 (m, 2, vinyl).

[α] $_{\text{D}}^{21}$: +0.37° (C 0.715, CH_3OH).

REFERENTIAL EXAMPLE 4

15 Synthesis of 11,15-bis(t-butyldimethylsilyl)-
prostaglandin $\text{F}_{2\alpha}$ methyl ester:-

11,15-bis(t-butyldimethylsilyl)-5,6-dehydro-
prostaglandin $\text{F}_{2\alpha}$ methyl ester (28.7 mg; 0.048 mmole) was
20 dissolved in benzene (1 ml), and cyclohexane (1 ml) and
Linder catalyst (28.7 mg) were added. The mixture was
stirred at 22 to 23.5°C for 12 hours in an atmosphere of
hydrogen. The catalyst was removed by filtration. The
filtrate was washed with ethyl acetate. The organic layers
25 were combined and concentrated under reduced pressure.

The concentrate was chromatographed on a silica
gel column (6 g, ethyl acetate:hexane:benzene=1:15:2) to
give 11,15-bis(t-butyldimethylsilyl)prostaglandin $\text{F}_{2\alpha}$
methyl ester (23.2 mg, 81%).

30 TLC: Rf=0.32 (ethyl acetate:hexane=1:5)

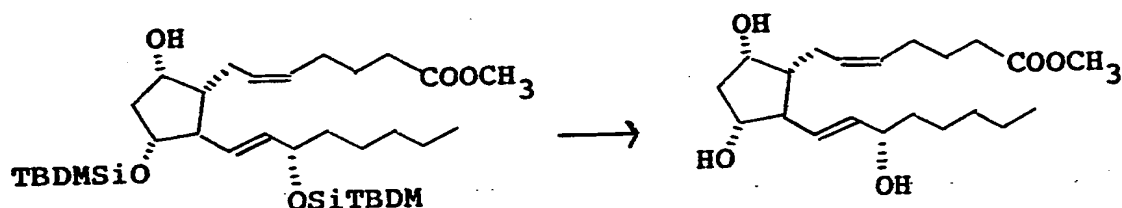
- 42 -

IR (liquid film):

3610-3280, 1745, 1250, 1000, 970, 938, 830 and
770 cm^{-1} . ^1H NMR (CDCl_3) δ :

5 0.03 and 0.05 (each s, 12, $\text{SiCH}_3 \times 4$),
 0.8-1.0 (m, 21, $\text{C-CH}_3 \times 7$),
 1.2-2.4 (m, 20, CH_2CO , $\text{CH}_2 \times 6$, $\text{CH}_2\text{C} = \times 2$,
 and $\text{CH} \times 2$),
 2.69 (d, 1, $J=9.5\text{Hz}$, OH), 3.67 (s, 3, OCH_3),
 10 4.05 (br, 3, $\text{CHO} \times 3$), 5.40 (m, 2, vinyl).
 $[\alpha]_D^{23}$: $+12.3^\circ$ ($\underline{\text{C}} 1.037$, CH_3OH).

REFERENTIAL EXAMPLE 5

Synthesis of prostaglandin $\text{F}_{2\alpha}$ methyl ester:-

15 11,15-bis(t-butyldimethylsilyl)prostaglandin $\text{F}_{2\alpha}$
 methyl ester (21 mg, 0.035 mmole) was dissolved in acetic
 acid (1 ml), and H_2O (0.33 ml) and THF (0.1 ml) were added.
 The mixture was stirred at 55°C for 1.5 hours. The mixture
 was transferred to a large vessel, and toluene was added.
 20 The mixture was concentrated under pressure several times
 to remove acetic acid and H_2O . The residue was chromato-
 graphed on a silica gel column [3 g, ethyl acetate-hexane
 (1:1) \rightarrow (1:0), gradient] to give (+)- $\text{PGF}_{2\alpha}$ methyl ester
 (11 mg, 85%).

25 TLC: $\text{Rf}=0.2$ (ethyl acetate:cyclohexane:THF=6:3:1)

IR (liquid film):

3640-3040, 1738, 1435, 1160, 1116, 1042, 1020,
968 and 858 cm^{-1} . ^1H NMR (CDCl_3) δ :

30 0.89 (t, s, $J=6.5\text{Hz}$, CH_3),
 1.2-2.4 (m, 20, CH_2CO , $\text{CH}_2 \times 6$, $\text{CH}_2\text{C} = \times 2$,
 and $\text{CH} \times 2$),

- 43 -

2.57 (br, 1, OH), 3.29 (br, 1, OH),
3.69 (s, 3, OCH₃), 4.03 (brm, 3, CHO x 3),
5.3-5.6 (m, 2, vinyl).

¹³C NMR (CDCl₃) δ:

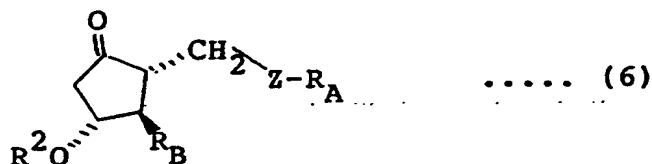
5 14.0, 22.6, 24.8, 25.2, 25.6, 26.6, 31.8, 33.5,
 37.3, 43.0, 50.5, 51.6, 55.8, 72.9, 73.0, 78.0,
 129.1, 129.6, 132.6, 135.3, 174.3

[α]_D²⁰: +31.4° (c 0.423, CH₃OH).

10 The spectral data (IR, ¹H NMR, ¹³C NMR, TLC) of the
 product completely agreed with those of (+)-PGF_{2α} methyl
 ester derived from (+)-PGF_{2α}.

What is claimed is:

1. A process for producing a 2,3-disubstituted-4-substituted cyclopentanone represented by the formula

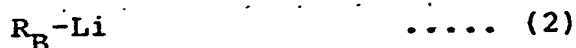


R^2 represents a tri(C_1 - C_7)hydrocarbon silyl group or R^2O represents an acetal linkage, R_B represents a substituted or unsubstituted C_2 - C_{10} alkyl or alkenyl group, Z represents an ethylene, ethynylene, trans-vinylene, cis-vinylene, phenylene or phenyleneoxa group, and R_A represents a hydrogen atom or a substituted or unsubstituted C_1 - C_7 alkyl or alkenyl group, an enantiomorph thereof, or a mixture of these in an arbitrary ratio, which comprises

(A) subjecting a 4-substituted-2-cyclopentenone represented by the following formula



wherein R^2 is as defined above, an enantiomorph thereof, or a mixture of these in an arbitrary ratio, and an organocopper compound formed from an organolithium compound represented by the following formula



wherein R_B is as defined above, and a copper compound represented by the following formula



wherein Q represents a halogen atom, a cyano group, a phenylthio group or a 1-pentynyl group,

- 45 -

to conjugate addition-reaction, and thereafter,

(B) reacting the resulting enolate intermediate with a halide represented by the following formula



wherein Z and R_A are as defined above, and X represents a halogen atom or a tosyl group, in the presence of an organotin compound represented by the following formula

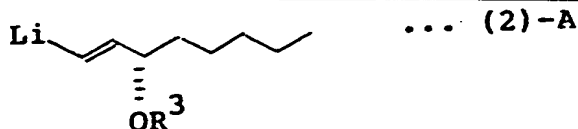


wherein R's are identical or different and each represents a C_1-C_4 alkyl group, a C_3-C_7 cycloalkyl group, a phenyl group or a halogen atom provided that two or three R's cannot be halogen atoms at the same time, and Y represents a halogen atom or a triflate group.

2. The process of claim 1 wherein in the organolithium compound represented by formula (2), R_B is a substituted or unsubstituted C_2-C_{10} alkenyl group, and the substituent on the alkenyl group is a C_1-C_4 alkyl group, a C_3-C_7 cycloalkyl group, a C_2-C_4 alkynyl group, a phenyl group, a phenoxy group, a C_1-C_4 alkoxy group, or the group OR^2 in which R^2 is as defined above, provided that the phenyl and phenoxy groups may further be substituted by fluoro, methyl, trifluoromethyl or trifluoromethoxy.

3. The process of claim 1 wherein in the organolithium compound represented by formula (2), R_B is a substituted or unsubstituted C_2-C_{10} alkyl group, and the substituent on the alkyl group is a C_3-C_7 cycloalkyl group, a vinyl group, a C_2-C_4 alkynyl group, a phenyl group, a phenoxy group, a C_1-C_4 alkoxy group or the group OR^2 in which R^2 is as defined above, provided that the phenyl and phenoxy groups may further be substituted by fluoro, methyl, trifluoromethyl or trifluoromethoxy.

formula



wherein R^3 is a tri(C_1 - C_7)hydrocarbon silyl group or OR^3 represents an acetal linkage.

5. The process of claim 1 wherein in the organotin compound represented by formula (4), R's are identical or different and each represents a butyl, cyclohexyl or phenyl group.

6. The process of claim 1 wherein the halide represented by formula (5) is represented by the following formula



wherein X is as defined above in formula (5), R¹ represents a C₁-C₁₀ alkyl group, a substituted or unsubstituted phenyl group, a substituted or unsubstituted C₃-C₇ cycloalkyl group or a substituted or unsubstituted phenyl (C₁-C₂)alkyl group, and n is an integer of 1 to 9.

7. The process of claim 1 wherein the halide of formula (5) is represented by the following formula



wherein X is as defined above, and Z' represents an ethynylene, trans-vinylene, cis-vinylene, phenylene or phenyleneoxa group, and R'_A represents a C₁-C₇ alkenyl group whose position remotest from the group Z' is substituted by the substituent -COOR¹ in which R¹ is as defined.

8. The process of claim 1 wherein the halide of formula (5) is an iodide.

- 47 -

9. The process of claim 1 wherein the conjugate addition reaction in step (A) is carried out in the presence of a trivalent organophosphorus compound.

10. The process of claim 1 wherein the enolate intermediate formed by the conjugate addition reaction in step (A) is reacted with the halide (5) in the presence of the organotin compound (4) in step (B) in an aprotic polar solvent.